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(21) International Application Number: PCT/US93/10640 (22) International Filing Date: 4 November 1993 (04.11.93) (30) Priority data: 971,882 5 November 1992 (05.11.92) US (60) Parent Application or Grant (63) Related by Continuation US 971,882 (CIP) Filed on 5 November 1992 (05.11.92) (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : DEMPSKI, Robert, E. [US/US]; 1629 Arran Way, Dresher, PA 19025 (US). OLIVERO, Robert, C. [US/US]; 683 Monroe Avenue, Ardsley, PA 19038 (US). SCHOTZ, Edward, C. [US/US]; 1620 Jennifer Lane, Blue Bell, PA 19422 (US). (74) Agent: BIGLEY, Frank, P.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (81) Designated States: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KR, KZ, LK, LV, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: DRUG DELIVERY DEVICE (57) Abstract The instant invention is directed to a means of processing and delivering to a patient, medicaments, whose exposure control limits are equal to or less than 0.1 mg/m ³ , in a manner which assures protection of those preparing the dosage form and patient and health care professionals who come in contact with the product.		

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- 1 -

TITLE OF THE INVENTION
DRUG DELIVERY DEVICE

5 This case is a continuation-in-part of U.S. Serial No.
08/018/912 which was filed on February 17, 1993; which is a
continuation of U.S. Serial No. 07/802,000 which was filed on
December 3, 1991.

10 BACKGROUND OF THE INVENTION

Pharmaceutical scientists are rapidly increasing their
understanding of disease at the molecular level. As a result, many of
the pharmaceutical medicaments which are now available to treat
humans and other animals are highly potent and useful only in low
dosages. That is, exposure to the medicament, at levels which have
15 traditionally been considered the "no effect" level for many drugs, may
lead to very serious side effects, including death. For this reason,
conventional procedures may require extensive modifications if they are
to be used to produce dosage forms containing these highly potent
substances.

20 Oral dosage forms such as tablets and capsules are
convenient for the patient to transport and offer the best chance for
patient compliance with the prescribed medication regiment. However,
since traditional solid dosage forms utilize powder mixing or dry
granulation compressing, these forms represent one of the most difficult
25 and potentially dangerous medicaments to produce. During processing,
inhalation is considered the primary route of exposure. However,
ingestion by swallowing large inhaled particles which impact on the
mucociliary system of the respiratory tract is likely. Ingestion by
contamination of hands, dermal contact and transdermal absorption are
30 also possible routes for unintentional receipt of some medicaments.

In addition to the production employee, there is a further
risk to the patient, health care professionals and others who come in
contact with the product, due to inadvertent contact with the active
ingredient.

- 2 -

Liquid preparations which contain these highly potent compounds are considerably easier to control. Once the active ingredient is dissolved in an appropriate solvent, the chance for accidental contamination, at a level which would cause harm, is dramatically reduced. However, liquid preparations are not as convenient to use, may taste harsh and may result in poor patient compliance.

In order to overcome the problems associated with the production and use of solid dosage forms containing highly potent compounds, Applicants have created a novel coated dosage form, wherein the active ingredient is contained within a coating, which is applied to a core, in a quantitative and reproducible process. Using this technology, the medicament is contained within a liquid until it has been applied to the carrier core as a film coating. The film coating mixture both fixes the medicament on the surface of the core and seals the surface so that the chance of active ingredient flaking off the dosage form is greatly reduced. When even greater protection is desired, the film coated core may be further sealed with an overcoat. This additional coating provides an extra level of protection for those who subsequently handle the dosage form.

BRIEF DESCRIPTION OF THE INVENTION

This invention concerns a dosage form and a method of making the dosage form, for the delivery of highly potent medicaments to humans or other animals comprising:

- (a) a carrier core; and
- (b) a coating which comprises a highly potent medicament; wherein, the coating which comprises the highly potent medicament and a coating material, adheres to the surface of the carrier core fixing the medicament to the surface of the core and entraining the medicament.

Optionally, a protective overcoating may be added to the dosage form to provide further protection.

- 3 -

The Class III antiarrhythmic drugs: methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure I);
5 methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydronaphth-2-yl)-3,4-dihydro-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure II); and
10 methanesulfonamide, N-[1'-[2-(5-benzofurazanyl)ethyl]-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, monohydrochloride, (structure III) are examples of highly potent drugs that can be delivered using this device.

A BRIEF DESCRIPTION OF THE DRAWINGS

15 Figure 1 shows a block diagram of the process steps utilized in the production of the novel dosage form designed to deliver highly potent drugs.

DETAILED DESCRIPTION OF THE INVENTION

20 This invention discloses a dosage form and a method of making the dosage form, for the delivery of highly potent drugs to humans or other animals comprising:

- (a) a carrier core; and
- (b) a coating which comprises a highly potent medicament;
25 wherein, the coating which comprises the highly potent medicament and a coating material, adheres to the surface of the carrier core fixing the medicament to the surface of the core and entraining the medicament.

30 This invention concerns a method for the safe manufacture and delivery to humans and other animals in need thereof, of highly potent medicaments by dispersing the medicament in a coating mixture, spraying the coating mixture on a carrier core and optionally overcoating the coated core with a protective over-coating. The entire coating operation may be conducted within a closed system where the medicament may be contained.

- 4 -

The phrase "dosage form" includes, but is not limited to tablets, capsules, spheronized particles, coated non-pareil seeds, boluses, pills, disks, lozenges, controlled delivery devices and any other regularly shaped solid dosage form.

5 Although any medicament is considered within the scope of this invention, this novel dosage form provides for a particularly safe and effective means to deliver highly potent or highly toxic medicaments, defined as those medicaments which have an Exposure Control Limit of about 0.1 mg/m^3 or less. These medicaments include
10 inorganic and organic compounds without limitation, including medicaments that act on the peripheral nerves, ion channels, nuclear receptors, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood
15 circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone systems, immunological system, reproductive system, skeletal systems, autocoid systems, alimentary and excretory systems, inhibitory and histamine systems, and those materials that act on the central nervous system such as hypnotics and sedatives.

20 Examples of beneficial drugs are disclosed in Remington's Pharmaceutical Sciences, 16th Ed., 1980, published by Mack Publishing Co., Eaton, Pa.; and in The Pharmacological Basis of Therapeutics, by Goodman and Gilman, 6th Ed., 1980, published by the MacMillan Company, London; and in The Merck Index, 11th Edition, 1989,
25 published by Merck & Co., Rahway, N.J. The drug can be in various forms, such as charged molecules, charged molecular complexes, ionizable salts or neutral molecules. Acceptable salts include, but are not limited to hydrochlorides, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrate, borate, acetate, maleate, malate,
30 tromethamine, tartrate, oleate, salicylate, salts of metals, and amines or organic cations, for example quaternary ammonium.

Derivatives of medicaments such as esters, ethers and amides without regard to their ionization and solubility characteristics can be used alone or mixed with other medicaments. Also, a medicament can be used in a form that upon release from the device, is

- 5 -

converted by enzymes, hydrolyzed by body pH or other metabolic processes to the parent form, or to a biologically active form.

Exposure Control Limits are based on pharmacological considerations and defined as the time-weighted average concentration for a normal 8 hour workday and 40 hour workweek to which nearly all workers may be repeatedly exposed day after day without adverse effect. To facilitate the derivation of a numerical limit, the equation shown below has been reported. (See E.V. Sargent and G. D. Kirk, "Establishing Airborne Exposure Control Limits in the Pharmaceutical Industry", Am. Ind. Hyg. Assoc. J., 49(6): 309 - 313, 1988, which is hereby specifically incorporated by reference.)

$$\text{ECL (mg/m}^3\text{)} = \frac{\text{NOEL (mg/kg/day)} \times \text{BW (kg)}}{\text{V (m}^3\text{/day)} \times \text{S (days)} \times \text{a} \times \text{SF}}$$

15

$$\text{V (m}^3\text{/day)} \times \text{S (days)} \times \text{a} \times \text{SF}$$

Where NOEL is the no-observable-effect-level, BW is the average human body weight (70 kg for males; 50 kg for females); V is the volume of air breathed in an 8 hour day (10 m³/day); S is the time to achieve a plasma steady state; SF is a safety factor; and a is the percent of the compound absorbed.

This concept of exposure limits is based on the principle that exposure to a chemical agent may be permitted up to some tolerance limit greater than zero. This assumes a nonlinear dose-response relationship and allows for the estimation of a NOEL. Generally, the NOEL is based on either the therapeutic effect for which the drug is intended or on one or more clinically recognizable side effects which can occur at or below the therapeutic level.

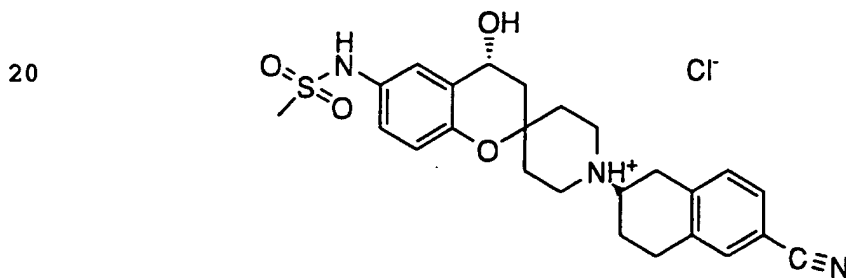
Generally, the NOEL is determined in populations where it is associated with a certain amount of variability. Individual variability in response to a drug may be due to differences in age, sex, health and nutritional status or genetic factors. When variability within a species is known to be large, a safety factor, usually up to 10 fold, can be used. A 10 fold safety factor also can be used when the NOEL has not been

- 6 -

identified and the lowest observable effect dose is used. Larger safety factors (100 to 1000 fold) generally are reserved for risk estimated or inconclusive human data or animal data. The larger safety factors may be applied to compounds with carcinogenic or teratogenic potential.

5 Exposure Control Limits of 0.5 ug/m³ have been calculated for the Class III antiarrhythmic drugs:

methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure I);
10 methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-naphth-2-yl)-3,4-dihydro-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure II); and
methanesulfonamide, N-[1'-[2-(5-benzofurazanyl)ethyl]-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, monohydrochloride,
15 (structure III). This very low exposure control limit makes these medicaments particularly suited for this dosage form and processing.

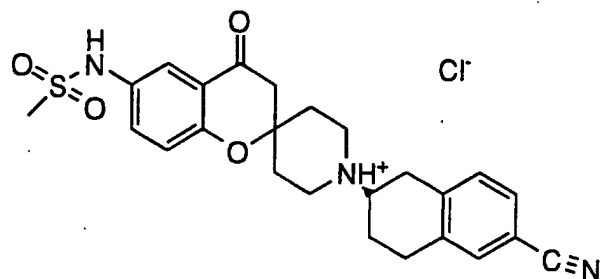


Structure I

30

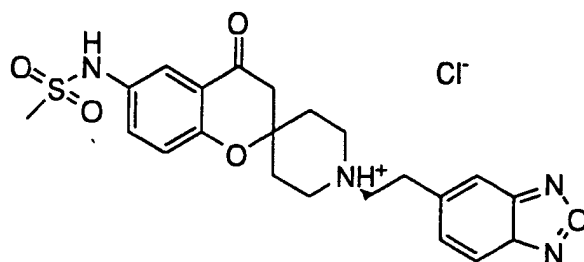
- 7 -

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Structure II



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Structure II

20 The above list of pharmaceutical products and medicaments is not meant to be exhaustive. Many other compounds will certainly work in the instant invention and are included within the scope of this invention.

25 The novel dosage form and process of the instant invention may be used to deliver medicament to humans or other animals. The term "animal" includes mammals, humans and primates, such as domestic, household, sport or farm animals such as dogs, sheep, goats, cattle, horses and pigs, laboratory animals such as mice, rats and guinea pigs, fish, avians, reptiles and zoo animals.

30 By "carrier core" is meant a nucleus upon which a mixture containing the medicament may be applied. The carrier core may be, for example, a non-pareil seed, a compressed tablet, a triturate, a spheronized particle, an inert bead and slugged material. This list is not meant to be in any way inclusive of the carrier cores which are included within the scope of this invention.

- 8 -

When the particle size of the carrier core is considered important, the carrier cores may be sized by passing them through a screen which has a pore size at the upper diameter limit and collecting the carrier cores on a screen which has a pore size at the lower diameter limit. For example, when non-pareil seeds are used, the seeds are generally sized by collecting those seeds which pass through a #25 mesh size screen and are collected on a #30 mesh size screen. This results in a more uniform particle size for the finished product.

The carrier core may be composed of lactose and other excipients such as magnesium stearate, microcrystalline cellulose, starch, stearic acid, calcium phosphate, glycerol monostearate, sucrose, polyvinylpyrrolidone, gelatin, methylcellulose, sodium carboxymethylcellulose, sorbitol, mannitol, polyethylene glycol and other ingredients commonly utilized as stabilizing agents or to aid in the production of tablets, spheronized particles, or other carrier core forms mentioned above.

The carrier core may also contain, within the core, a second medicament. For example, cardiovascular agents such as Class I antiarrhythmic compounds, anti-anginal compounds, vasodilators, potassium supplements, β -adrenergic receptor blocking agents, sodium channel blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, A II receptor antagonists, and diuretics may be delivered in combination with the compounds of structures I, II or III, by including them within the carrier core.

The coating containing the highly potent medicament may also include hydroxypropylmethylethylene glycols, sodium carboxymethyl cellulose, carboxymethyl cellulose, methacrylate hydrogels, cellulose acetate phthalate, polyvinyl alcohol, polyacrylic acid, poly N-vinyl pyrrolidone, polyacrylamide, polyethylene oxide, methylhydroxyethyl cellulose, ethyl cellulose, povidone, shellac, gelatin, wax, acacia, methylcellulose, methacrylic acid, methacrylic acid ester copolymers, titanium dioxide, talc, colorants, plasticizers and other soluble ingredients commonly used in film coatings of pharmaceutical dosage forms.

- 9 -

The medicament coating may be prepared as a solution in water or an organic solvent. The medicament coating may also be prepared as a slurry, a suspension, a dispersion and may be partially or completely solubilized prior to application. The medicament may be
5 mixed with a binder, dispersant, lubricants, emulsifier, diluent, wetting agent and colorants.

The overcoat may include hydroxypropylmethyl-cellulose, hydroxypropylcellulose, polyethylene glycols, sodium carboxymethyl cellulose, carboxymethyl cellulose, methacrylate
10 hydrogels, cellulose acetate phthalate, polyvinyl alcohol, polyacrylic acid, poly N-vinyl pyrrolidone, polyacrylamide, polyethylene oxide, methylhydroxyethyl cellulose, ethyl cellulose, povidone, shellac, gelatin, wax, acacia, methylcellulose, methacrylic acid, methacrylic acid ester
15 copolymers, titanium dioxide, talc, colorants, plasticizers and other soluble ingredients commonly used in film coatings of pharmaceutical dosage forms.

The overcoat may be prepared as a solution in water, an aqueous solution or an organic solvent. The overcoating may also be prepared as a slurry, suspension, dispersion and may be partially or
20 completely solubilized prior to application. In general the film coating mixture is prepared by mixing a solution containing from about 1 mg to about 500 mg of the highly potent compound and about 140 ml of water with about 0.6 to about 10 grams of hydroxypropylmethylcellulose in about 50 ml of water. However, more or less concentrated solutions of
25 the highly potent compound or the hydroxypropylmethylcellulose are within the scope of this invention.

The medicament coating and the overcoat may be applied to the dosage form core using any coating procedure including the use of a fluidized bed film coating device, including a roto-processor, a pan
30 coater or a baffled pan coater or any air suspension process. The film coating mixture may also be manually added to the carrier cores while they are mixed in the presence of a heated stream of air or inert gas.

In general the medicament coating and the overcoat may be applied to any thickness desired. However, a coating thickness of from

- 10 -

about 1 to about 1000 mm is generally applied to the surface of the dosage form core. In the preferred embodiment using a non-pareil seed as a carrier core, a coating thickness of from about 5 to about 100 mm is applied depending upon the concentration of medicament to be included on each carrier core. When tablets are used as the carrier core, the film coating thickness generally ranges from about 25 to about 500 mm, depending upon the concentration of medicament to be included on each carrier core.

10

EXAMPLE 1

Capsules containing non-pareil seed coated with a solution containing the Class III antiarrhythmic drug methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride were prepared using the following procedure.

15

Preparation of the Binder Solution

In a suitable tared, clean, dry, glass beaker, 100 g of purified water was heated to 80°C. To this heated solvent, 200 g of hydroxypropylmethylcellulose was added slowly with vigorous stirring. The container was removed from the heat source and while stirring at low speed, 100 g of unheated purified water was added.

20

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Overcoat Preparation

A portion, 44 g, of the binder solution was weighed into a clean, tared 250 ml erlenmeyer flask. This solution was diluted with 110 g of purified water with mixing. The resulting diluted solution was covered and stored at room temperature until needed.

30

Raw Material Preparation

A quantity of non-pareil seeds were sized between #25 and #30 mesh sieves. From the sized non-pareil seeds, 452.8 g were transferred to a holding container.

- 11 -

Magnesium stearate was bolted through a #60 screen. One gram was transferred to a suitable storage container until needed.

About 100 g of empty capsules (H.G. #3, white opaque 999) were weighed and transferred to a suitable storage device.

Manufacturing Conditions

In a class III glovebox, 120.75 mg of methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride was transferred to a vessel with 140 ml of water and mixed for one hour with shaking. To this solution was added with stirring, 66 g of the binder solution which had been previously prepared. This mixture was transferred to a 4 inch in diameter Wurster Coating Column. The coating column conditions were as follows:

Preheat column for about 10 minutes

Atomization Pressure set to about 1.1 Bar

Inlet Temperature set to about 70°C

Outlet Temperature set to about 34°C

Air Flow set to about 80 m³/hour

Inner Partition Height set to about 0.5 inches

Application Rate set to about 5.0 g/min.

Next, 452.8 g of the sized non-pareil seeds were loaded into the coating column and the polymeric/drug solution was applied. The pellets were dried for 10 minutes in the column.

Once the coating operation was completed, the overcoat was applied. The binder solution was sprayed onto the coated pellets using the same coating conditions used to apply the drug containing coat. Following application of the overcoat, the pellets were dried for 15 minutes in the column.

The dried coated non-pareils were transferred into a double plastic bag containing 1 g of the bolted magnesium stearate. The bag was sealed after allowing a head space of air and then vigorously shaken to sufficiently lubricate the coated pellets.

- 12 -

The lubricated pellets were then encapsulated using a Bonapace Hand Fill Encapsulator. The weight of pellets in each capsule was based on a laboratory analysis of the pellets after coating.

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EXAMPLE 2

Placebo tablet can be used as carrier cores, in place of non-pareil seeds. Tablets can be prepared from dry blending a mixture of about 35% microcrystalline cellulose, about 50% lactose and about 14% pregelatinized starch. This mixture is then lubricated with magnesium stearate (about 1% of final tablet weight) and directly compressed into the core tablet using a standard tableting machine.

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These tablets may then be transferred to a film coating processor where the medicament coating and if desired the overcoat is added.

EXAMPLE 3

Exemplary of the many formulations that are included within the scope of this invention are the following:

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- 13 -

EXAMPLE 3(a)

	Ingredient	Amount/ Unit
5	L-706,000-001-T-012 (Incorporate Coating Loss)	2.530 mg
	L-706,000-001-T-012 (Equivalent to 2.0 mg Base)	2.30 mg
10	Non-Pareil Seeds White (25-30 mesh)	224.2 mg
	Hydroxypropylmethylcellulose 6cps	5.0 mg
	Water Purified	(gm)
	Magnesium Stearate	0.5 mg
15	TARGET FILL WEIGHT	232.0 mg
	Capsule Hard Gelatin # 3 White	46.5 mg
	Opaque 999	
	TARGET CAPSULE WEIGHT	278.5 mg

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- 14 -

EXAMPLE 3(b)

	Ingredient	Amount/ Unit
5	L-706,000-001-T-012 (Incorporate Coating Loss)	2.415 mg
	L-706,000-001-T-012 (Equivalent to 2.0 mg Base)	2.300 mg
10	Non-Pareil Seeds White (25-30 mesh)	224.2 mg
	Hydroxypropylmethylcellulose 6cps	2.5 mg
	Hydroxypropylcellulose LF Grade	2.5 mg
	Water Purified	(gm)
15	Acetone NF	(gm)
	Magnesium Stearate	0.5 mg
	TARGET FILL WEIGHT	232.0 mg
	Capsule Hard Gelatin # 3 White	46.5 mg
20	Opaque 999	
	TARGET CAPSULE WEIGHT	278.5 mg

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- 15 -

EXAMPLE 3(c)

	Ingredient	Amount/ Unit
5	L-706,000-001-T-012 (Includes Coating Loss)	2.5715 mg
	L-706,000-001-T-012 (Equivalent to 2.0 mg Base)	2.30 mg
10	Lactose NF Anhydrous	117.0 mg
	Cellulose Microcrystalline NF	80.0 mg
	AVICEL 102	
	Magnesium Stearate NF	1.0 mg
15	Crosscarmellose Sodium NF	2.0 mg
	Type A	
	Hydroxypropylmethylcellulose 6cps	2.30 mg
	Hydroxypropylcellulose LF Grade	2.30 mg
	Water Purified	(gm)
	Acetone NF	(gm)
20	Hydroxypropylmethylcellulose 6cps	3.25 mg
	Hydroxypropylcellulose LF Grade	3.25 mg
	Titanium Dioxide USP	0.280 mg
	Talc USP Purified	0.100 mg
25	Blue FD&C # 2 Aluminum Lake (14 % Dye)	0.025 mg
	Water Purified	(gm)
	Theoretical Tablet Weight	213.81 mg

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- 16 -

EXAMPLE 3(d)

	Ingredient	Amount/ Unit
5	L-706,000-001-T-012 (Incorporate Coating Loss)	2.415 mg
	L-706,000-001-T-012 (Equivalent to 2.0 mg Base)	2.300 mg
10	NonPareil Seeds White (25-30 mesh)	224.2 mg
	Hydroxypropylmethylcellulose 6cps	2.5 mg
	Hydroxypropylcellulose LF Grade	2.5 mg
	Water Purified	(gm)
	Acetone NF	(gm)
15	Sodium Lauryl Sulfate	0.375 mg
	Magnesium Stearate	0.125 mg
	TARGET FILL WEIGHT	232.0 mg
	Capsule Hard Gelatin # 3 White	46.5 mg
	Opaque 999	
20	TARGET CAPSULE WEIGHT	278.5 mg

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- 17 -

EXAMPLE 3(e)

	Ingredient	Amount/ Unit
5	L-706,000-001-T-012 (Incorporate Coating Loss)	0.06038 mg
	L-706,000-001-T-012 (Equivalent to 2.0 mg Base)	0.0575 mg
10	Non-Pareil Seeds White (25-30 mesh)	226.4 mg
	Hydroxypropylmethylcellulose 6cps	2.5 mg
	Hydroxypropylcellulose LF Grade	2.5 mg
	Water Purified	(gm)
15	Acetone NF	(gm)
	Sodium Lauryl Sulfate	0.375 mg
	Magnesium Stearate	0.125 mg
	TARGET FILL WEIGHT	232.0 mg
20	Capsule Hard Gelatin # 3 White	46.5 mg
	Opaque 999	
	TARGET CAPSULE WEIGHT	278.5 mg

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- 18 -

EXAMPLE 3(f)

	Ingredient	Amount/ Unit
5	L-706,000-001-T-012	11.5 mg
	(Equivalent to 2.0 mg Base)	
	Lactose NF Anhydrous	117.0 mg
	Cellulose Microcrystalline NF	80.0 mg
10	AVICEL 102	
	Magnesium Stearate NF	1.0 mg
	Crosscarmellose Sodium NF	2.0 mg
	Type A	
	Hydroxypropylmethylcellulose 6cps	6.00 mg
15	Hydroxypropylcellulose LF Grade	6.00 mg
	Water Purified	(gm)
	Acetone NF	(gm)
	Hydroxypropylmethylcellulose 6cps	3.25 mg
	Hydroxypropylcellulose LF Grade	3.25 mg
20	Titanium Dioxide USP	0.280 mg
	Talc USP Purified	0.100 mg
	Blue FD&C # 2 Aluminum Lake	0.025 mg
	(14 % Dye)	
	Water Purified	(gm)
25	Theoretical Tablet Weight	230.41 mg

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- 19 -

WHAT IS CLAIMED IS:

1. A dosage form for the delivery of highly potent medicaments to humans or other animals comprising:
- 5 (a) a carrier core; and
(b) a coating which comprises a highly potent medicament and a coating material;
wherein, the coating adheres to the surface of the carrier core fixing the medicament to the surface of the core and entraining
10 the medicament.
2. The dosage form of Claim 1, wherein an overcoat comprising a coating material is applied after the medicament containing coating.
- 15 3. The dosage form of Claim 1, wherein the medicament is selected from the group consisting of the Class III antiarrhythmic drugs:
methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-
20 naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure I);
methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydronaphth-2-yl)-3,4-dihydro-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure II); and
25 methanesulfonamide, N-[1'-[2-(5-benzofurazanyl)ethyl]-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, monohydrochloride, (structure III).
- 30 4. The dosage form of Claim 2, wherein the medicament is selected from the group consisting of the Class III antiarrhythmic drugs:
methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure I);

- 20 -

methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydronaphth-2-yl)-3,4-dihydro-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure II); and
5 methanesulfonamide, N-[1'-[2-(5-benzofurazanyl)ethyl]-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, monohydrochloride, (structure III).

5. The dosage form of Claim 1, wherein the carrier
10 core is selected from the group consisting of a non-pareil seed, a compressed tablet, a triturate, a spheronized particle, an inert bead and slugged material.

6. The dosage form of Claim 2, wherein the carrier
15 core is selected from the group consisting of a non-pareil seed, a compressed tablet, a triturate, a spheronized particle, an inert bead and slugged material.

7. The dosage form of Claim 5, wherein the
20 compressed tablet comprises, pregelatinized starch, microcrystalline cellulose, lactose, and magnesium stearate.

8. The dosage form of Claim 6, wherein the
25 compressed tablet comprises, pregelatinized starch, microcrystalline cellulose, lactose and magnesium stearate.

9. The dosage form of Claim 1, wherein the cellulosic coating comprises hydroxypropylmethylcellulose.

10. The dosage form of Claim 2, wherein the cellulosic
30 coating comprises hydroxypropylmethylcellulose.

11. The dosage form of Claim 1, wherein the overcoat comprises hydroxypropylmethylcellulose.

- 21 -

12. The dosage form of Claim 2, wherein the overcoat comprises hydroxypropylmethylcellulose.

5 13. The dosage form of Claim 1, wherein the coated non-pareil seeds are contained within a gelatin capsule.

14. The dosage form of Claim 2, wherein the coated and overcoated non-pareil seeds are contained within a gelatin capsule.

10 15. The dosage form of Claim 1, wherein the coated non-pareil seeds are further compressed into a tablet.

15 16. The dosage form of Claim 2, wherein the coated and overcoated non-pareil seeds are further compressed into a tablet.

17. The dosage form of Claim 1, wherein the coated spheronized particles are contained within a gelatin capsule.

20 18. The dosage form of Claim 2, wherein the coated and overcoated spheronized particles are contained within a gelatin capsule.

19. The dosage form of Claim 1, wherein the coated spheronized particles are compressed into a tablet.

25 20. The dosage form of Claim 2, wherein the coated and overcoated spheronized particles are compressed into a tablet.

30 21. The dosage form of Claim 1, wherein the coated slugged material is contained within a gelatin capsule.

22. The dosage form of Claim 2, wherein the coated and overcoated slugged material is contained within a gelatin capsule.

- 22 -

23. The dosage form of Claim 1, wherein the coated slugged material is compressed into a tablet.

5 24. The dosage form of Claim 2, wherein the coated and overcoated slugged material is compressed into a tablet.

10 25. The dosage form of Claim 1, wherein the carrier core contains a medicament selected from the group of cardiovascular agents consisting of Class I antiarrhythmic compounds, anti-anginal compounds, vasodilators, potassium supplements, β -adrenergic receptor blocking agents, sodium channel blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, A II receptor antagonists, and diuretics.

15 26. The dosage form of Claim 2, wherein the carrier core contains a medicament selected from the group of cardiovascular agents consisting of Class I antiarrhythmic compounds, anti-anginal compounds, vasodilators, potassium supplements, β -adrenergic receptor blocking agents, sodium channel blockers, calcium channel blockers, 20 angiotensin converting enzyme inhibitors, A II receptor antagonists, and diuretics.

25 27. A method of preparing a dosage form for the delivery of highly potent medicaments to humans or other animals, comprising the steps of:

- (a) preparing a film coating mixture comprising the highly potent medicament by dispersing the highly potent medicament in a suitable solvent;
- (b) preparing the carrier core to receive the coating material;
- 30 (c) applying the film coating mixture of (a) to the carrier core; and
- (d) drying the film coating mixture on the surface of the carrier core.

- 23 -

28. A method of preparing a dosage form for the delivery of highly potent medicaments to humans or other animals, comprising the steps of:

- 5 (a) preparing a film coating mixture comprising the highly potent medicament by dispersing the highly potent medicament in a suitable solvent;
- (b) preparing the carrier core to receive the coating material;
- (c) applying the film coating mixture of (a) to the carrier core;
- 10 (d) drying the film coating mixture on the surface of the carrier core;
- (e) preparing the overcoating material;
- (f) applying the overcoating material to the coated carrier core; and
- 15 (g) drying the overcoating material on the surface of the coated carrier core.

29. The process of Claim 27, wherein the film coating mixture is prepared by mixing a solution containing from about 1 mg to about 500 mg of the highly potent compound and about 140 ml of water with about 0.6 to about 10 grams of hydroxypropylmethylcellulose in about 50 ml of water.

30. The process of Claim 28 wherein the film coating mixture is prepared by mixing a solution containing from about 1 mg to about 500 mg of the highly potent compound and about 140 ml of water with about 0.6 to about 10 grams of hydroxypropylmethylcellulose in about 50 ml of water.

31. The process of Claim 27, wherein the carrier cores are non-pareil seeds which are prepared by collecting those seeds which pass through a #25 mesh size screen and are collected on a #30 mesh size screen.

- 24 -

32. The process of Claim 28, wherein the carrier cores are non-pareil seeds which are prepared by collecting those seeds which pass through a #25 mesh size screen and are collected on a #30 mesh size screen.

5

33. The process of Claim 27, wherein the carrier cores are tablets comprising excipients selected from the group consisting of lactose, pregelatinized starch, magnesium stearate, microcrystalline cellulose, and starch.

10

34. The process of Claim 28, wherein the carrier cores are tablets comprising excipients selected from the group consisting of lactose, pregelatinized starch, magnesium stearate, microcrystalline cellulose, and starch.

15

35. The process of Claim 27, wherein the medicament is selected from the group consisting of the Class III antiarrhythmic drugs: methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure I); methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydronaphth-2-yl)-3,4-dihydro-4-oxo-spiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure II); and methanesulfonamide, N-[1'-[2-(5-benzofurazanyl)ethyl]-3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-monohydrochloride, (structure III).

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36. The process of Claim 28, wherein the medicament is selected from the group consisting of the Class III antiarrhythmic drugs: methanesulfonamide N-[1'-(6-cyano-1,2,3,4-tetrahydro-2(R)-naphthalenyl)-3,4-dihydro-4(R)-hydroxyspiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-, monohydrochloride, (structure I);

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- 25 -

methanesulfonamide, N-[1'-(6-cyano-1,2,3,4-tetrahydronaphth-2-yl)-
3,4-dihydro-4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-, (+)-,
monohydrochloride, (structure II); and
5 methanesulfonamide, N-[1'-[2-(5-benzofurazanyl)-ethyl]3,4-dihydro-
4-oxospiro[2H-1-benzopyran-2,4'-piperidin]-6-yl]-monohydrochloride,
(structure III).

37. The process of Claim 27, wherein the overcoat
10 material comprises hydroxypropylmethylcellulose or hydroxypropyl-
cellulose or both.

38. The process of Claim 28, wherein the overcoat
material comprises hydroxypropylmethylcellulose, hydroxypropyl-
15 cellulose or both.

39. The process of Claim 27, wherein the coat containing
the medicament ranges from about 1 to about 1000 mm in thickness.

40. The process of Claim 28, wherein the coat containing
20 the medicament ranges from about 1 to about 1000 mm in thickness.

41. The process of Claim 31, wherein the coat containing
the medicament ranges from about 5 to about 100 mm when it is applied
25 to a non-pareil seed.

42. The process of Claim 33, wherein the coat containing
the medicament ranges from about 25 to about 500 mm when it is
30 applied to a tablet.

1/1

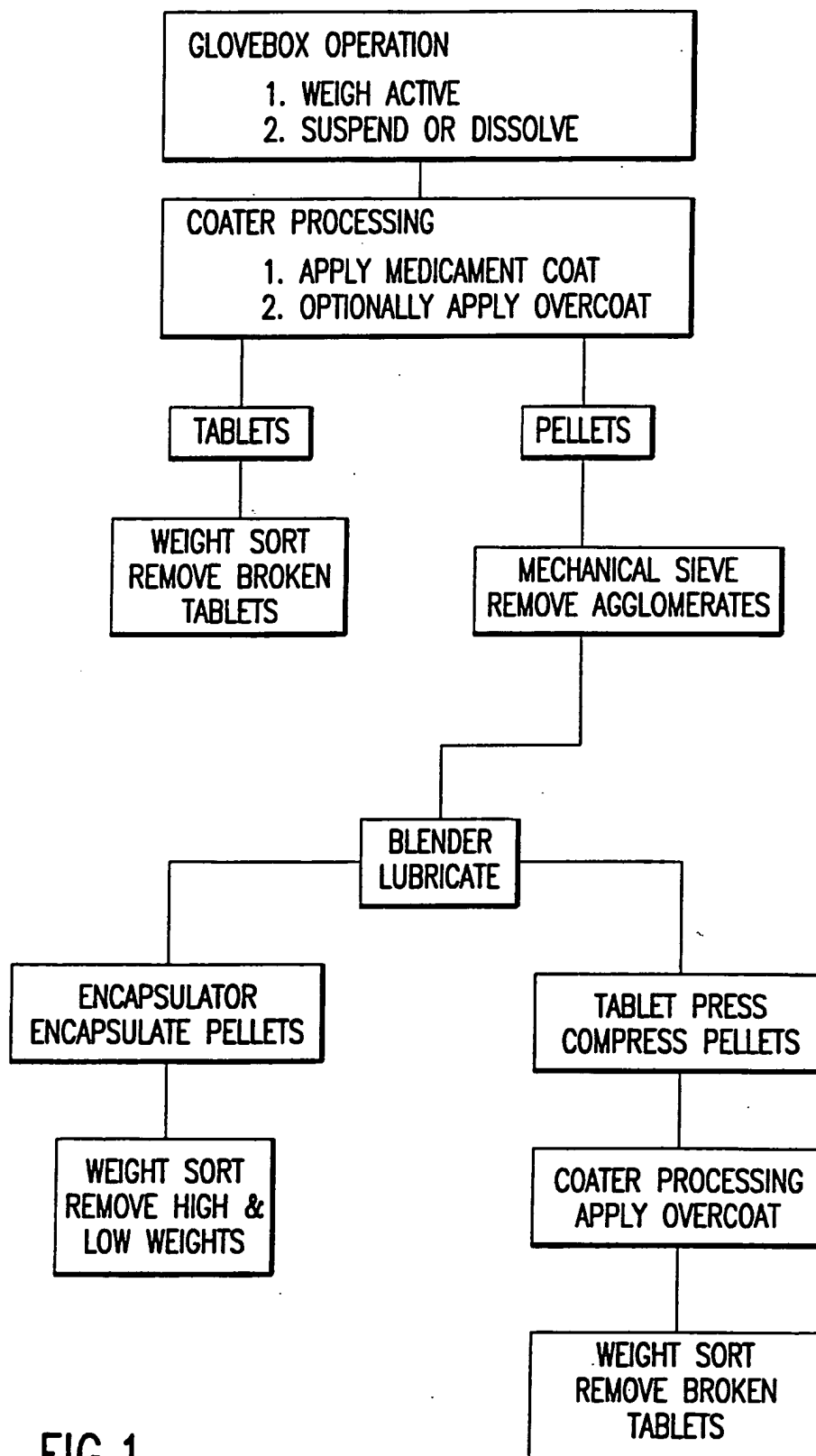


FIG.1

INTERNATIONAL SEARCH REPORT

Intern. application No.

PCT/US93/10640

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/64

US CL :424/456

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/456, 454, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,082,669 (SHIRAI) 21 JANUARY 1992; See entire document.	1-42
P, Y	US, A, 5,215,989 (BALDWIN) 01 JUNE 1993; See entire document.	1-42



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

11 JANUARY 1994

Date of mailing of the international search report

24 FEB 1994

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